CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	June 8, 2012
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
BLA #	125409
Applicant Name	Genentech, Inc.
Date of Submission	December 6, 2011
PDUFA Goal Date	June 8, 2012
Proprietary Name / Established (USAN) Name	Perjeta/ Pertuzumab
Dosage Forms / Strength	420 mg/14 mL (30 mg/mL) single-use vial
Proposed Indication(s)	PERJETA is indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Gideon Blumenthal, Nancy Scher
Statistical Reviews	Somesh Chattopadhyah, Shenghui Tang
Pharmacology Toxicology Reviews	Kimberly Ringgold, Anne Pilaro, John Leighton
OBP Reviews	Kathyrn King, L. Graham, Kimberly Rains
Microbiology Review	Bo Chi, Colleen Thomas
Clinical Pharmacology Review	Pengfei Song, Kevin Krudys, Christian Grimstein
DPDP	Marybeth Toscano, Michelle Safarik
OSI	Robert Young
CDTL Review	Patricia Cortazar
OSE/DMEPA	Jibril Abdus-Samad (2), Kimberly DeFronzo
OSE/Div Epidemiology I & II	Stephen Chang, Holly Epperly
PMHS Consult	Melissa Tassinari
IRT-QT Consultation	Jiang Liu
CDRH/OIVD	Kevin Lorick

OND = Office of New Drugs
DPDP = Division of Professional Drug Promotion
OSE = Office of Surveillance and Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
OSI = Office of Scientific Investigations
DDRE = Division of Drug Risk Evaluation
DRISK = Division of Risk Management
CDTL = Cross-Discipline Team Leader
IRT-QT = Interdisciplinary Review Team for QT Studies
N/A = not applicable

Division Director Summary Review

1. Introduction

This original Biologics License Application (BLA) for Perjeta™ (pertuzumab) Injection is dated December 6, 2011, and was received on December 8, 2012. The proposed indication is "for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease." This review will summarize the efficacy and safety data supporting approval, the recommendations of each review discipline, and the risk benefit assessment.

2. Background

The product and its mechanism of action are summarized in the following excerpts from the agreed-upon package insert.

> Pertuzumab is a recombinant humanized monoclonal antibody that targets the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2). Pertuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture containing the antibiotic, gentamicin…
>
> Pertuzumab targets the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2) and, thereby, blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3 and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two major signal pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signaling pathways can result in cell growth arrest and apoptosis, respectively. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).
>
> While pertuzumab alone inhibited the proliferation of human tumor cells, the combination of pertuzumab and trastuzumab significantly augmented anti-tumor activity in HER2-overexpressing xenograft models.

The regulatory history is summarized from the CDTL Review.

- Pre-IND meeting: May 3, 2001
- IND submission: June 2001

- End-of-Phase 2 meeting: April 17, 2007. The design of the CLEOPATRA trial (WO20698/TOC4129g) was discussed.
- Type C meeting: November 5, 2007. The trial and its statistical analysis plan were discussed.
- Type C meeting: May 24, 2011. Format and content of the BLA were discussed.
- Pre-BLA meeting: September 30, 2011. The efficacy and safety results from the CLEOPATRA trial were discussed.

3. CMC/Device

The CMC review from the Division of Monoclonal Antibodies made the following recommendations on approvability:

Recommendation on Traditional Elements:
During inspection of the drug substance manufacturing site and in subsequent discussions of data submitted with respect to failures of cell growth, it became apparent that the drug substance manufacturing process is not currently in a state of control (see section 3.2.S.2.3.3 of this review "Cell Culture Investigation"). Following discussions with the Agency, the Sponsor has initiated three concurrent plans to resolve the cell growth issues associated with manufacturing: 1) manufacturing from the MCB; 2) developing a new WCB and manufacturing from this new WCB; and 3) manufacturing using a modified process from WCB (b) (4) Any one of these approaches might be sufficient in the short term to support a validated process for the manufacture of pertuzumab drug substance, however currently there is not a validated process. Process validation is a legally enforceable requirement under section 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B)) and FDA regulations require that process validation procedures be established and followed (§ 211.100) before a batch can be distributed (§§ 211.22 and 211.165). **As the Sponsor does not have a validated process, from a CMC perspective, it is not possible to recommend approval of this license at this time.** Based on information provided by the Sponsor, (b) (4) If along with associated process validation study data these are acceptable, the process could be validated for manufacture from the MCB. This appears to be the fastest mechanism available. Therefore, it is recommended that FDA extend the review clock for 3 months via a major amendment mechanism based on a major amendment received in May to allow this exercise to be completed and the data to be reviewed by the Agency. If the review clock cannot be extended, a Complete Response letter is recommended, as data have not been provided that support the Sponsor's ability to consistently manufacture pertuzumab by a validated process.

Unfortunately, the applicant has refused to make this product available through an expanded access program to patients prior to licensure, which could have been a mechanism whereby seriously ill patients could obtain pertuzumab whilst the manufacturing issues were being addressed. Out of concern for the seriously ill patients who stand to benefit from this therapy for an unmet medical need, the clinical division

has indicated they intend to approve this product within a time frame consistent with the PDUFA deadline and to resolve outstanding manufacturing issues post-licensure. A meeting was held with the Center Director on May 18, 2012, who agreed that because the conformance lots that were manufactured in 2010 prior to the cell culture failures allow for (b) (4) supply of pertuzumab (as estimated by the Sponsor) of acceptable quality, and because this product is for a life-threatening condition and there is an unmet medical need for this product, the CMC concerns regarding validation of the drug substance manufacturing process would be handled as Post Marketing Requirements. Therefore, DMA has participated in drafting of PMRs as the only remaining mechanism to mitigate risks to product quality from a process which lacks adequate validation. A list of these PMRs is provided below under III, "List of Deficiencies to be communicated".

(b) (4)

As results of the review (b) (4) of the submission, there were 2 post marketing requirements (PMRs) and 1 post marketing commitment (PMC). These are PMRs #6 and #7 and PMC #1 under section III below, "List of Deficiencies to be communicated".

The Quality Team Leader's Executive Summary provides the following recommendations and conclusions on approvability.

The Division of Monoclonal Antibodies (DMA), Office of Biotechnology Products, OPS, CDER, does not currently recommend approval of STN 125409 for Pertuzumab manufactured by Genentech. The data submitted in this application are inadequate to support the conclusion that the manufacture of Pertuzumab is well controlled and consistently leads to a product that is pure and potent.

DMA recommends that FDA extend the review clock for 3 months via a major amendment mechanism based on any one of a series of submissions received during May, 2012. The CMC team believes this is potentially the fastest pathway to an adequately supported approval of the BLA. This would be expected to enable the applicant to complete their assessment (root cause analysis) of manufacturing problems and determine whether the problems are due to cell bank and/or other process issues, and to determine/define a modified manufacturing process that is appropriately supported with data.

> If the review clock will not be extended, DMA's recommendation is a Complete Response (CR) letter, since data have not been provided consistent with a valid commercial manufacturing process.
>
> Based on the understanding that the applicant has refused to make this product more widely available to patients prior to licensure while the manufacturing issues are being addressed, the clinical review office has indicated their intent to approve this product within a time frame consistent with the PDUFA deadline and to resolve outstanding manufacturing issues post-licensure. To the knowledge of the CMC review team, the initial licensure of a biological product under a BLA without concurrent approval of the manufacturing facility and the manufacturing process is unprecedented. This approach was agreed upon by the CDER Director. Therefore, DMA participated in the drafting of PMRs as the only mechanism available to mitigate risks to product quality from a process which lacks adequate validation.

DMA's concerns about product manufacturing are based on cell culture failures that were identified during the inspection, revealing a loss of control since the manufacture of the validation lots. The circumstances are described below in the following excerpt from the review.

> Five registration batches from the 2010 campaign were manufactured without incident in 2010. However, at the pre-approval inspection of the Vacaville facility in March, 2012, while reviewing discrepancy reports, the DMA reviewers on site became aware that (b) (4) to initiate the Q1/Q2 pertuzumab 2012 campaign had been discontinued due to poor cell viability or growth. (b) (4) . It was determined that these observations would be further evaluated as a review issue, as an investigation to identify the root cause of these failures was ongoing. Additionally, because WCB (b) (4) is maintained by the (b) (4) facility, a root cause attributed to the WCB (b) (4) would be out of scope of the Vacaville inspection.
>
> In a series of communications between the Agency and Genentech following the inspection, it became clear that Genentech had no plans to investigate cell bank stability as a root cause of these failures. Following a series of teleconferences, Genentech agreed to the following actions to allow data necessary to potentially resolve the lack of control over the cell growth process within the PDUFA timeline: characterize product manufactured from thaws exhibiting (b) (4) to ensure no changes in product quality; assess the stability of the MCB (b) (4) through their ability to thaw (b) (4) at the Vacaville facility; and generate a new working cell bank. These approaches were predicated on the understanding that the culture failures were limited (b) (4)

[redacted] (b) (4)

[redacted] (b) (4) The CMC review team believed that these data, along with the associated process validation data, could potentially provide sufficient additional information to support licensure of this BLA. As this appeared to be the fastest mechanism available for BLA approval, the CMC team recommended to the clinical group that FDA extend the review clock for 3 months via a major amendment mechanism based on a major amendment received in May to allow this exercise to be completed and the data to be reviewed by the Agency. In ensuing discussions with the clinical team, the CMC review team was informed that these concerns would be overruled in a BLA approval action in order to allow distribution of the available and suitable drug product lots. Therefore, the division provided the requested language for the needed information to be provided through a post-approval regulatory requirement (refer to section III of this review).

The claim for categorical exclusion was deemed acceptable.

The review stated that the following should be communicated in the letter regarding the dating period.

> The dating period for pertuzumab shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be 24 months from the date of manufacture when stored at -20°C. We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

The microbiology review of the drug substance made the following recommendation:

> The drug substance part of this application is recommended for approval from product quality microbiology perspective with three post-market commitments (PMCs, see below).
>
> The BLA is not recommended for approval to manufacture pertuzumab drug substance in the Genentech Vacaville, CA facility under the U.S. License 1048. This is the recommendation from the DGMPA/OMPQ documented in the final TB-EER for BLA 125409.

The review clarified that "A pre-license inspection was conducted at the Vacaville facility on 3/20-28/12. DGMPA/OMPQ recommended withhold the approval of the BLA based on the

recent cell culture failures in the Pertuzumab manufacturing campaign and the inability of consistently manufacturing at the Vacaville facility."

The microbiology review of drug product stated that "The drug product portion of the BLA was reviewed from a product quality microbiology perspective and is recommended for approval."

OIVD/CDRH reviewed the HER2 testing devices and the proposed labeling of pertuzumab in regard to HER2 testing during review of (b) (4) and proposed revisions to section 5.4 of the package insert. These revisions have been incorporated into the agreed-upon package insert.

I concur with the manufacturing concerns raised in the CMC and Microbiology reviews and in the TB-EER. However, the risks of a potential drug shortage must be weighed against the benefit that this product can provide to patients now (see section 13, Risk Benefit Assessment). The product from the 2010 manufacturing campaign is not affected by the current manufacturing issues and Genentech estimates that based on their projections it should be sufficient for a (b) (4) supply. This approval will be only for the product that was manufactured in 2010. The applicant has agreed to a number postmarketing commitments that are designed to determine the root cause of the manufacturing issues, to mitigate the risk a shortage of pertuzumab, and to plan for a drug shortage should it occur (see section 13, Postmarketing Requirements and Postmarketing Commitments) .

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology BLA Review and Evaluation stated that "The nonclinical studies submitted to this BLA provide sufficient information to support the use of pertuzumab for the treatment of patients with HER2-positive metastatic or locally recurrent, unresectable breast cancer" and provided the following summary of nonclinical findings.

> Pharmacology
> Pertuzumab (rhuMab 2C4) is a recombinant humanized monoclonal antibody against the HER2/neu receptor (also referred to as ErbB2). The amino acid homology of human and monkey ErbB2 was 99%. Therefore, the cynomolgus monkey was selected as the appropriate model for nonclinical evaluation. Tumor growth was inhibited by pertuzumab at doses of 30 – 90 mg/kg in the Founder 2-134R tumor xenograft model, which is resistant to trastuzumab. Pertuzumab also exhibited anti-tumor activity in 1/6 of the mammary cancer models, 1/4 of the ovarian, and 4/18 of the NSCLC cancer models. Both pertuzumab and trastuzumab as single agents were significantly active against HER2 overexpressing (3^+) Calu-3 non-small cell lung cancer (NSCLC) xenografts [85% and 82% tumor growth inhibition (TGI), respectively]. The combination of pertuzumab and trastuzumab was greater in activity (100 % TGI) compared to either single agent effect.

Pharmacokinetics

The PK profile of pertuzumab was studied in the monkey; the nonclinical species used for the chronic toxicology and fetal toxicity studies. Pertuzumab was eliminated from plasma with a half-life of approximately 10 days. The plasma clearance and volume of distribution following intravenous administration were low (clearance = 5 mL/day/kg and volume of distribution, Vss = 70 ml/kg). Following subcutaneous administration, the peak plasma level (t_{max}) was reached within 2.28 days and rhuMab 2C4 was slowly eliminated from plasma with a half-life of approximately 10 days. The subcutaneous bioavailability was 81.5%.

Following intravenous administration of pertuzumab to monkeys for 26 weeks, pertuzumab exposures increased in a dose-proportional manner. Faster clearance was observed in the 150 mg/kg dose group. Serum pertuzumab concentrations increased in a dose-proportional manner between all doses tested in pregnant monkeys and fetuses. Ratios of fetal to maternal pertuzumab levels were comparable (0.294, 0.399, and 0.338, respectively).

General Toxicity

The toxicological profile of pertuzumab suggests that pertuzumab appears to be well-tolerated in monkeys. Nonclinical findings show toxicities in the lung and gastrointestinal tract, which are expect given the distribution of the HER2/neu antigen.

Reproductive and Developmental Toxicity

Pertuzumab caused fetal lethality in pregnant monkeys treated with loading doses of ≥ 30 mg/kg followed by bi-weekly doses ≥ 10 mg/kg (approximately 0.2 to 2-fold greater than the exposure at the recommended human dose, by AUC). Fetal effects were also noted at doses ≥ 30/10 mg/kg. Malformations were observed at doses ≥ 100/33.3 mg/kg dose; the highest dose level tested was approximately 2.-fold higher than the recommended dose for patients. These malformations included paw hyperextension/hyperflexion, microtia, small lungs, thin walls in the ventricular regions of the heart, fused caudal and sacral vertebra, and supernumerary lumber vertebra. Thus, administration of pertuzumab during pregnancy may pose a risk to the human fetus.

Special Toxicity

Pertuzumab did not cause lysis of cynomolgus monkey or human erythrocytes and was compatible with cynomolgus monkey and human serum and plasma in in vitro test systems. Cell surface staining with pertuzumab in human tissues was noted in the haired skin, placenta, parathyroid gland, tonsil, mammary gland, ureter, and urinary bladder tissues. Cytoplasmic staining was noted in the salivary gland and prostate gland as well as in the stomach, haired skin, and thymic cyst of human tissues. In monkey tissues, cell surface staining was noted in the sweat and sebaceous gland, mammary gland, placenta, ureter, urinary bladder, and prostate gland. Cytoplasmic staining was noted in adenohypophysis and salivary gland.

The secondary and tertiary pharm/tox reviewers concurred with the primary reviewer's recommendations.

I concur with the pharmacology/toxicology reviewers that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review stated that this BLA is acceptable from a clinical pharmacology perspective and provided the following summary of pertuzumab's clinical pharmacology.

> Pertuzumab demonstrated linear pharmacokinetics (PK) at a dose range of 2-25 mg/kg. With the proposed dosing regimen, steady-state concentration of pertuzumab was reached following the first maintenance dose. A population PK analysis estimated clearance and terminal elimination half-life of pertuzumab as 0.235 L/day and 18 days, respectively. Baseline serum albumin level and lean body weight as covariates only exerted a minor influence on PK parameters. Therefore, no dose adjustments based on body weight or baseline albumin level are needed. Based on the population PK analysis, dose adjustments are not needed for renal impairment. No significant drug interactions were observed when pertuzumab was co-administered with docetaxel and trastuzumab, as well as with other chemotherapeutic agents (gemcitabine, capecitabine, or erlotinib). No large changes in mean QTc intervals (i.e., > 20 ms) were detected at the proposed pertuzumab dosing regimen.
>
> The incidence of positive anti-therapeutic antibodies (ATAs) to pertuzumab was 2.8% in the pertuzumab arm as compared to 6.2% in the placebo arm. The presence of ATAs had no known association with hypersensitivity reactions and anaphylaxis. Although the presence of ATAs appeared to be associated with shorter PFS and lower response rate, the benefit of pertuzumab treatment seemed to be preserved within both ATA-positive and ATA-negative subgroups.

I concur with the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

The design and efficacy results of the CLEOPATRA trial that provides the basis for approval are summarized in the following excerpt from the agreed-upon package insert.

> The randomized trial was a multicenter, double-blind, placebo-controlled trial of 808 patients with HER2-positive metastatic breast cancer. Breast tumor specimens were required to show HER2 overexpression defined as 3+ IHC or FISH amplification ratio ≥ 2.0 determined at a central laboratory. Patients were randomized 1:1 to receive placebo plus trastuzumab and docetaxel or PERJETA plus trastuzumab and docetaxel. Randomization was stratified by prior treatment (prior or no prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy) and geographic region (Europe, North America, South America, and Asia). Patients with prior adjuvant or neoadjuvant therapy were required to have a disease-free interval of greater than 12 months before trial enrollment.
>
> PERJETA was given intravenously at an initial dose of 840 mg, followed by 420 mg every 3 weeks thereafter. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks thereafter. Patients were treated with PERJETA and trastuzumab until progression of disease, withdrawal of consent, or unacceptable toxicity. Docetaxel was given as an initial dose of 75 mg/m^2 by intravenous infusion every 3 weeks for at least 6 cycles. The docetaxel dose could be escalated to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. At the time of the primary analysis, the mean number of cycles of study treatment administered was 16.2 in the placebo-treated group and 19.9 in the PERJETA-treated group.
>
> The primary endpoint of the randomized trial was progression-free survival (PFS) as assessed by an independent review facility (IRF). PFS was defined as the time from the date of randomization to the date of disease progression or death (from any cause) if the death occurred within 18 weeks of the last tumor assessment. Additional endpoints included overall survival (OS), PFS (investigator-assessed), objective response rate (ORR) and duration of response.
>
> Patient demographic and baseline characteristics were balanced between the treatment arms. The median age was 54 (range 22 to 89 years), 59% were White, 32% were Asian, and 4% were Black. All were women with the exception of 2 patients. Seventeen percent of patients were enrolled in North America, 14% in South America, 38% in Europe, and 31% in Asia. Tumor prognostic characteristics, including hormone receptor status (positive 48%, negative 50%), presence of visceral disease (78%) and non-visceral disease only (22%) were similar in the study arms. Approximately half of the patients received prior adjuvant or neoadjuvant anti-HER2 therapy or chemotherapy (placebo 47%, PERJETA 46%). Among patients with hormone receptor positive tumors, 45% received prior adjuvant hormonal therapy and 11% received hormonal therapy for metastatic disease. Eleven percent of patients received prior adjuvant or neoadjuvant trastuzumab.

The randomized trial demonstrated a statistically significant improvement in IRF-assessed PFS in the PERJETA-treated group compared with the placebo-treated group [hazard ratio (HR) = 0.62 (95% CI: 0.51, 0.75), p < 0.0001] and an increase in median PFS of 6.1 months (median PFS of 18.5 months in the PERJETA-treated group vs. 12.4 months in the placebo-treated group) (see Figure 1). The results for investigator-assessed PFS were comparable to those observed for IRF-assessed PFS.

Consistent results were observed across several patient subgroups including age (< 65 or ≥ 65 years), race, geographic region, prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no). In the subgroup of patients with hormone receptor-negative disease (n=408), the hazard ratio was 0.55 (95% CI: 0.42, 0.72). In the subgroup of patients with hormone receptor-positive disease (n=388), the hazard ratio was 0.72 (95% CI: 0.55, 0.95). In the subgroup of patients with disease limited to non-visceral metastasis (n=178), the hazard ratio was 0.96 (95% CI: 0.61, 1.52).

At the time of the PFS analysis, 165 patients had died. More deaths occurred in the placebo-treated group (23.6%) compared with the PERJETA-treated group (17.2%). At the interim OS analysis, the results were not mature and did not meet the pre-specified stopping boundary for statistical significance. See Table 2 and Figure 2.

Table 2 Summary of Efficacy from the Randomized Trial

Parameter	PERJETA + trastuzumab + docetaxel n=402	Placebo + trastuzumab + docetaxel n=406	HR (95% CI)	p-value
Progression-Free Survival (independent review)			0.62 (0.51, 0.75)	< 0.0001
No. of patients with an event	191 (47.5%)	242 (59.6%)		
Median months	18.5	12.4		
Overall Survival (interim analysis)			0.64 (0.47, 0.88)	0.0053*
No. of patients with an event	69 (17.2%)	96 (23.6%)		
Objective Response Rate (ORR)				
No. of patients analyzed	343	336		
Objective response (CR + PR)	275 (80.2%)	233 (69.3%)		
Complete response (CR)	19 (5.5%)	14 (4.2%)		
Partial Response (PR)	256 (74.6%)	219 (65.2%)		
Median Duration of Response (months)	20.2	12.5		

* The HR and p-value for the interim analysis of Overall Survival did not meet the pre-defined stopping boundary (HR ≤ 0.603, p ≤ 0.0012).

Figure 1 Kaplan-Meier Curve of IRF-Assessed Progression-Free Survival for the Randomized Trial

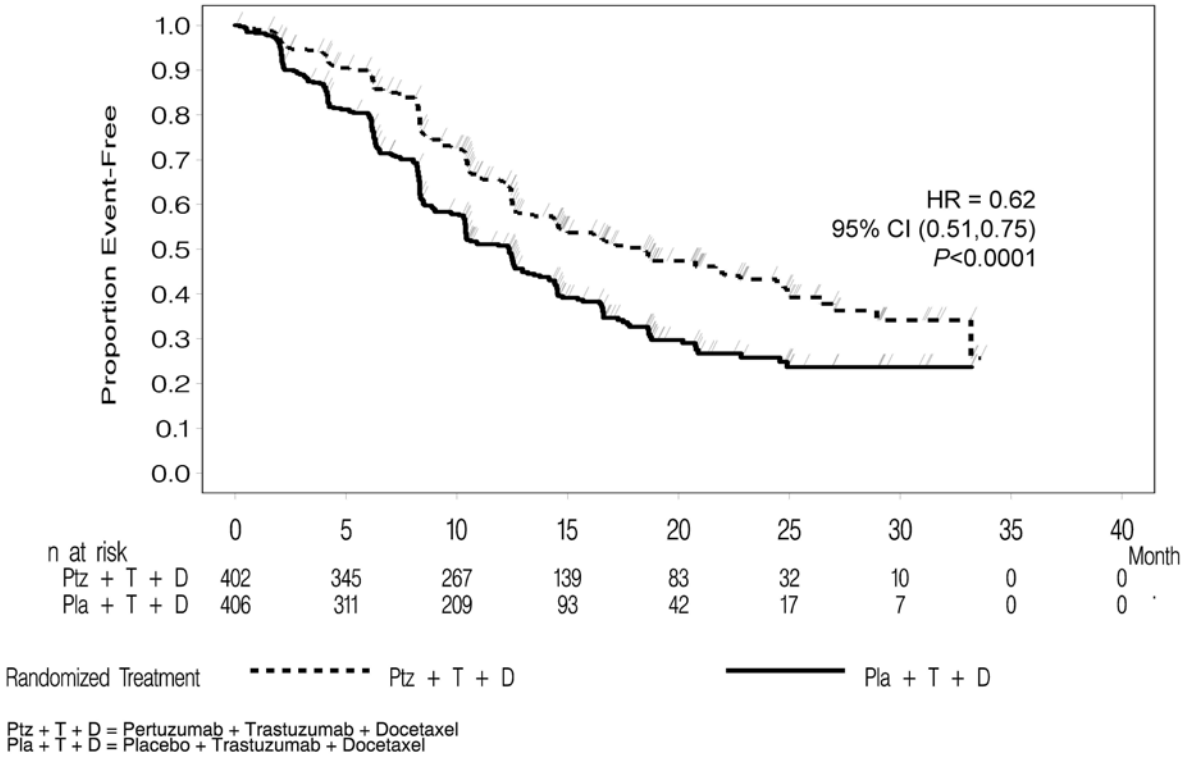
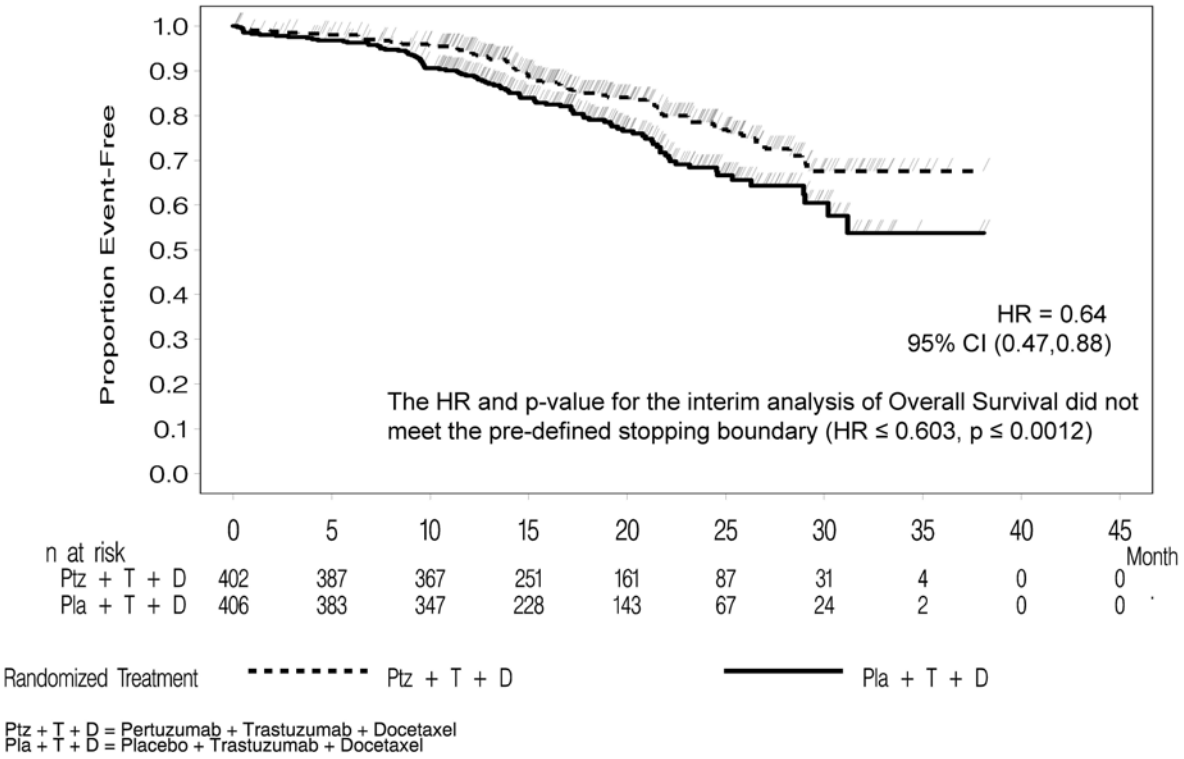


Figure 2 Kaplan-Meier Curve of Overall Survival for the Randomized Trial



8. Safety

The safety findings are summarized in the following excerpt from the agreed-upon package insert.

> In clinical trials, PERJETA has been evaluated in more than 1400 patients with various malignancies and treatment with PERJETA was predominantly in combination with other anti-neoplastic agents.
>
> The adverse reactions described in Table 1 were identified in 804 patients with HER2-positive metastatic breast cancer treated in the randomized trial. Patients were randomized to receive either PERJETA in combination with trastuzumab and docetaxel or placebo in combination with trastuzumab and docetaxel. The median duration of study treatment was 18.1 months for patients in the PERJETA-treated group and 11.8 months for patients in the placebo-treated group. No dose adjustment was permitted for PERJETA or trastuzumab. The rates of adverse events resulting in permanent discontinuation of all study therapy were 6.1% for patients in the PERJETA-treated group and 5.3% for patients in the placebo-treated group. Adverse events led to discontinuation of docetaxel alone in 23.6% of patients in the PERJETA-treated group and 23.2% of patients in the placebo-treated group. Table 1 reports the adverse reactions that occurred in at least 10% of patients in the PERJETA-treated group.
>
> The most common adverse reactions (> 30%) seen with PERJETA in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. The most common NCI - CTCAE (version 3) Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, leukopenia, diarrhea, peripheral neuropathy, anemia, asthenia, and fatigue. An increased incidence of febrile neutropenia was observed for Asian patients in both treatment arms compared with patients of other races and from other geographic regions. Among Asian patients, the incidence of febrile neutropenia was higher in the pertuzumab-treated group (26%) compared with the placebo-treated group (12%).

Table 1 Summary of Adverse Reactions Occurring in ≥ 10% of Patients on the PERJETA Treatment Arm in the Randomized Trial

Body System/Adverse Reactions	PERJETA + trastuzumab + docetaxel n=407 Frequency rate %		Placebo + trastuzumab + docetaxel n=397 Frequency rate %	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions				
Fatigue	37.6	2.2	36.8	3.3
Asthenia	26.0	2.5	30.2	1.5
Edema peripheral	23.1	0.5	30.0	0.8
Mucosal inflammation	27.8	1.5	19.9	1.0
Pyrexia	18.7	1.2	17.9	0.5
Skin and subcutaneous tissue disorders				
Alopecia	60.9	0.0	60.5	0.3
Rash	33.7	0.7	24.2	0.8
Nail disorder	22.9	1.2	22.9	0.3
Pruritus	14.0	0.0	10.1	0.0
Dry skin	10.6	0.0	4.3	0.0
Gastrointestinal disorders				
Diarrhea	66.8	7.9	46.3	5.0
Nausea	42.3	1.2	41.6	0.5
Vomiting	24.1	1.5	23.9	1.5
Constipation	15.0	0.0	24.9	1.0
Stomatitis	18.9	0.5	15.4	0.3
Blood and lymphatic system disorders				
Neutropenia	52.8	48.9	49.6	45.8
Anemia	23.1	2.5	18.9	3.5

Leukopenia	18.2	12.3	20.4	14.6
Febrile neutropenia*	13.8	13.0	7.6	7.3
Nervous system disorders				
Neuropathy peripheral	32.4	3.2	33.8	2.0
Headache	20.9	1.2	16.9	0.5
Dysgeusia	18.4	0.0	15.6	0.0
Dizziness	12.5	0.5	12.1	0.0
Musculoskeletal and connective tissue disorders				
Myalgia	22.9	1.0	23.9	0.8
Arthralgia	15.5	0.2	16.1	0.8
Infections and infestations				
Upper respiratory tract infection	16.7	0.7	13.4	0.0
Nasopharyngitis	11.8	0.0	12.8	0.3
Respiratory, thoracic and mediastinal disorders				
Dyspnea	14.0	1.0	15.6	2.0
Metabolism and nutrition disorders				
Decreased appetite	29.2	1.7	26.4	1.5
Eye disorders				
Lacrimation increased	14.0	0.0	13.9	0.0
Psychiatric disorders				
Insomnia	13.3	0.0	13.4	0.0

* In this table this denotes an adverse reaction that has been reported in association with a fatal outcome

The following adverse reactions were reported in < 10% of patients in the pertuzumab-treated group: paronychia (7.1% in the pertuzumab-treated group vs. 3.5% in the placebo-treated group), pleural effusion (5.2% in the pertuzumab -treated group vs. 5.8% in the placebo-treated group), left ventricular dysfunction (4.4% in the pertuzumab -treated group vs. 8.3% in the placebo-treated group) including symptomatic left ventricular systolic dysfunction (CHF)

(1.0% in the pertuzumab-treated group vs. 1.8% in the placebo-treated group), hypersensitivity (10.1% in the pertuzumab-treated group vs. 8.6% in placebo-treated group).

In the randomized trial, adverse reactions were reported less frequently after discontinuation of docetaxel treatment. All adverse reactions in the pertuzumab and trastuzumab treatment group occurred in < 10% of patients with the exception of diarrhea (19.1%), upper respiratory tract infection (12.8%), rash (11.7%), headache (11.4%), and fatigue (11.1%).

Patients in the randomized trial were tested at multiple time-points for antibodies to pertuzumab. Approximately 2.8% (11/386) of patients in the pertuzumab-treated group and 6.2% (23/372) of patients in the placebo-treated group tested positive for anti-pertuzumab antibodies. Of these 34 patients, none experienced anaphylactic/hypersensitivity reactions that were clearly related to the anti-therapeutic antibodies (ATA). The presence of pertuzumab in patient serum at the levels expected at the time of ATA sampling can interfere with the ability of this assay to detect anti-pertuzumab antibodies. In addition, the assay may be detecting antibodies to trastuzumab. As a result, data may not accurately reflect the true incidence of anti-pertuzumab antibody development.

There are four Warnings and Precautions. The first is that pertuzumab can cause fetal harm when administered to a pregnant woman. Treatment of pregnant cynomolgus monkeys with pertuzumab resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death. Similar findings have been seen clinically with trastuzumab which has a boxed warning. Because of the findings in cynomolgus monkeys and because pertuzumab is administered with trastuzumab, a boxed warning regarding the findings was included in the package insert. In addition, a pregnancy registry for women who become pregnant while receiving pertuzumab is a postmarketing requirement.

The second Warning and Precaution is regarding decreases in LVEF that have been reported with drugs that block HER2 activity, including pertuzumab. In the randomized trial, pertuzumab in combination with trastuzumab and docetaxel was not associated with increases in the incidence of symptomatic left ventricular systolic dysfunction (LVSD) or decreases in LVEF compared with placebo in combination with trastuzumab and docetaxel. Left ventricular dysfunction occurred in 4.4% of patients in the pertuzumab-treated group and 8.3% of patients in the placebo-treated group. Symptomatic left ventricular systolic dysfunction (congestive heart failure) occurred in 1.0% of patients in the pertuzumab-treated group and 1.8% of patients in the placebo-treated group. The package insert recommends assessments of LVEF prior to initiation of pertuzumab and at regular intervals (e.g., every three months) during treatment to ensure that LVEF is within the institution's normal limits. If LVEF is < 40%, or is 40% to 45% with a 10% or greater absolute decrease below the pretreatment value, pertuzumab and trastuzumab should be withheld and a repeat LVEF assessment should be performed within approximately 3 weeks. Pertuzumab and trastuzumab should be discontinued if the LVEF has not improved or has declined further, unless the benefits for the individual patient outweigh the risks.

The third Warning and Precaution concerns infusion and hypersensitivity reactions. The initial dose of pertuzumab was given the day before trastuzumab and docetaxel to allow for the

examination of PERJETA-associated reactions. On the first day, when only pertuzumab was administered, the overall frequency of infusion reactions was 13.0% in the pertuzumab-treated group and 9.8% in the placebo-treated group. Less than 1% were grade 3 or 4. The most common infusion reactions (≥ 1.0%) were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, and vomiting. During the second cycle when all drugs were administered on the same day, the most common infusion reactions in the pertuzumab-treated group (≥ 1.0%) were fatigue, dysgeusia, hypersensitivity, myalgia, and vomiting.

In the randomized trial, the overall frequency of hypersensitivity/anaphylaxis reactions was 10.8% in the pertuzumab-treated group and 9.1% in the placebo-treated group. The incidence of Grade 3 – 4 hypersensitivity/anaphylaxis reactions was 2% in the pertuzumab-treated group and 2.5% in the placebo-treated group according to National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI - CTCAE) (version 3). Overall, 4 patients in pertuzumab-treated group and 2 patients in the placebo-treated group experienced anaphylaxis.

The fourth Warning and Precaution concerns the need to assess HER2 status by laboratories with demonstrated proficiency in the specific technology being utilized.

9. Advisory Committee Meeting

The application was not referred to a meeting of the Oncologic Drugs Advisory Committee because outside expertise was not necessary; there were no controversial clinical issues that would benefit from advisory committee discussion.

10. Pediatrics

PeRC agreed with a full waiver of the pediatric study requirement for this application.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: The proprietary name of Perjeta was found to be acceptable.
- Physician labeling: agreement has been reached on the physician labeling. The major issue that was discussed is the need for a boxed warning for embryofetal death and birth defects.
- Carton and immediate container labels: agreement has been reached on carton and container labels
- Patient labeling/Medication guide: N/A

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  A statistically significant 6.1 month improvement in median progression-free survival (PFS) was observed in patients receiving pertuzumab compared to those receiving placebo [HR 0.62 (95% CI: 0.51, 0.75), p< 0.0001, log-rank test]. The median PFS was 18.5 and 12.4 months for patients on the pertuzumab and placebo arms, respectively. At the time of PFS analysis, a planned interim analysis for overall survival (OS) was performed [HR 0.64 (95% CI: 0.47, 0.88), p=0.0053]. However, the HR and p-value for the interim analysis of OS did not meet the pre-defined stopping boundary (HR ≤ 0.603, p ≤ 0.0012). The improvement in PFS is robust and clinically meaningful and was consistent across subgroups. In addition, the objective response rates were 80.2% in the pertuzumab arm and 69.3% in the placebo arm.

  The most common (> 30%) adverse reactions observed in patients receiving pertuzumab in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. The most common (> 2%) NCI – CTCAE (version 3) Grade 3 – 4 adverse reactions were neutropenia, febrile neutropenia, leukopenia, diarrhea, peripheral neuropathy, anemia, asthenia, and fatigue. Other significant adverse reactions reported with pertuzumab include left ventricular dysfunction, infusion-associated reactions, hypersensitivity reactions, and anaphylaxis. Pertuzumab in combination with trastuzumab and docetaxel was not associated with increases in the incidence of symptomatic left ventricular systolic dysfunction (LVSD) or decreases in left ventricular ejection fraction (LVEF) compared with placebo in combination with trastuzumab and docetaxel.

  Regarding CMC issues, the review team is concerned about the (b) (4) problems that occurred in the 2012 campaign, which could affect Genentech's ability to manufacture pertuzumab and their ability to continue to supply pertuzumab after it is launched. The Office of Manufacturing and Product Quality in CDER's Office of Compliance has recommended that we withhold approval of BLA 125409 (May 31, 2012 memorandum from Shawn Gould). Qualification lots of pertuzumab were successfully manufactured in 2010, and based on the Sponsor's estimates, a (b) (4) supply exists for patients.

  We have consulted with CDER's Office of Compliance regarding the inspectional findings of OMPQ. Ilisa Bernstein, Acting Director of the Office of Compliance, has reported that the problems observed during the 2012 campaign were not observed during the inspection with respect to the 2010 campaign. She further reported that

there were no observations made during the 2012 inspection that would lead us to believe there were any significant issues with the 2010 campaign. In addition, she reported the previous GMP surveillance inspection of this manufacturing facility was conducted by FDA's San Francisco District Office in June 2010. No form FDA 483 was issued, and the inspection was classified as no action indicated (NAI).

The Agency generally requires that the validation of the manufacturing process for a drug product be fully complete before approval of an application. In this case, we are taking the unusual step of approving only pertuzumab drug product that contains drug substance from Genentech's 2010 campaign prior to completion of the full demonstration of process validation for all pertuzumab manufacturing. We are approving this application in this manner based on: (1) our determination that product from the 2010 campaign meets all applicable requirements with respect to safety, purity, and potency; (2) that the (b) (4) problems in the 2012 campaign were not observed with the 2010 campaign, and no other significant issues were observed with respect to the 2010 campaign, and the facility received an NAI in 2010; (3) the applicant's commitment to undertake several steps to expeditiously resolve the (b) (4) problem; (4) the applicant's commitment to reduce and mitigate the risk of a drug shortage; and (5) our clinical determination that a compelling exigent public health need outweighs the risk of a future interruption in the drug's availability. The 6.1 month improvement in median PFS shown in the CLEOPATRA study suggests a meaningful clinical benefit to patients. Pertuzumab is the first dual antiHER2 therapy to be approved for the first-line treatment of metastatic breast cancer, and we would not like to delay its availability to patients pending resolution of CMC issues pertaining to production after the 2010 campaign. The marketing of additional production campaigns, including the 2012 campaign that experienced the (b) (4) problems, will be subject to further approval.

Steps to ensure a consistent drug supply and manufacturing process are outlined in the post-marketing obligations that the company has agreed to undertake. These include a plan for responding to potential pertuzumab shortage if attempts to re-establish the pertuzumab manufacturing process are unsuccessful or if demand is greater than anticipated. Genentech has agreed that the drug shortage plan will include communications to healthcare providers and patients, and it also will include a mechanism for ensuring that patients who are already receiving pertuzumab can continue to be treated according to the product label. Specific postmarketing requirements include conducting process validation studies under third party oversight to support further manufacture of pertuzumab.

I concur with the risk benefit assessments of the CDTL and the clinical reviewers.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

  Because of a signal of a serious risk of embryo-fetal toxicity, the postmarketing requirement is for a pregnancy registry. Postmarketing commitment 2 is for a plan for responding to potential pertuzumab shortages. Postmarketing commitments 3-14 are intended to address the manufacturing issues identified above and in section 3. Postmarketing commitment 15 is for submission of an ongoing clinical trial to test whether the addition of hormonal therapy increases the efficacy of pertuzumab-based therapy in the hormone receptor-positive, HER2-positive metastatic breast cancer population. Finally, postmarketing commitment 16 is for submission of the results of the planned final analysis of overall survival of the CLEOPATRA study.

Postmarketing Requirement

1. Establish a Pregnancy Registry to collect and analyze information for ten years on pregnancy complications and birth outcomes in women with breast cancer exposed to a pertuzumab-containing regimen within 6 months of conception or during pregnancy. Submit yearly interim reports, which may be included in your annual reports, on the cumulative findings and analyses from the Pregnancy Registry.

Draft Protocol Submission:	06/2012
Final Protocol Submission:	08/2012
Interim Report #1:	08/2013
Interim Report #2:	08/2014
Interim Report #3:	08/2015
Interim Report #4	08/2016
Interim Report #5	08/2017
Interim Report #6	08/2018
Interim Report #7	08/2019
Interim Report #8	08/2020
Interim Report #9	08/2021
Interim Report #10	08/2022
Study Completion:	08/2022
Final Report Submission:	08/2023

Postmarketing Commitments

2. Provide a plan for responding to potential pertuzumab shortages.

Draft Plan Submission:	07/2012
Final Plan Submission:	09/2012

3. Conduct a stability study that includes real time and stressed stability testing to assess the stability of the drug substance manufactured from thaws #4 and #6 of the Q1/Q2 2012 pertuzumab campaign. Provide a root cause analysis relating to the

cell bank issues. Submit the Interim and Final Reports as a Prior Approval Supplement (PAS).

Final Protocol Submission:	06/2012
Interim Report:	09/2012
Study Completion:	10/2014
Final Report:	12/2014

4. Conduct a process validation study to support manufacture of pertuzumab from the Master Cell Bank. Submit the Final Report as a PAS.

Study Completion:	12/2012
Final Report Submission:	02/2013

5. Conduct a process validation study to support manufacture of pertuzumab from a new Working Cell Bank. Submit the Final Report as a PAS.

Final Protocol Submission:	04/2013
Study Completion:	09/2014
Final Report Submission:	10/2014

6. Conduct process validation studies to support manufacture of pertuzumab from Working Cell Banks by a modified process. Submit the Final Report as a PAS.

Final Protocol Submission:	04/2014
Study Completion:	10/2015
Final Report Submission:	11/2015

7. Conduct stability studies of the Master Cell Bank at more frequent intervals than the currently proposed 10 years. Submit Interim Reports every four years and the Final Report after 20 years.

Final Protocol Submission:	09/2012
Interim Report 1:	06/2016
Interim Report 2:	06/2020
Interim Report 3:	06/2024
Interim Report 4:	06/2028
Final Report Submission:	06/2032

8. Reassess release and stability specifications for pertuzumab drug substance and drug product through June 30, 2014. Submit the Final Report as a Changes Being Effected-30 (CBE-30) supplement.

Study Completion:	12/2014
Final Report Submission:	03/2015

9. Conduct a study to assess the ability of a non-reduced CE-SDS assay to detect and quantitate pertuzumab fragmentation. Submit the Final Report as a CBE-30 supplement.

Final Protocol Submission:	09/2012
Study Completion:	07/2013
Final Report Submission:	09/2013

10. Conduct a study to establish a drug substance release specification to control for antibody-dependent cellular cytotoxicity (ADCC) activity of pertuzumab. Submit the Final Report as a PAS.

Study Completion:	02/2013
Final Report Submission:	03/2013

11. Conduct a study using end of production cells from commercial scale manufacturing that tests for *in vivo* adventitious viruses and genetic consistency. Submit the Final Report as a PAS.

Final Protocol Submission:	08/2012
Study Completion:	12/2012
Final Report Submission:	02/2013

12. Re-qualify the bioburden test for the bulk drug substance and in-process bioburden samples. Submit the Final Report as a CBE-0 supplement.

Final Protocol Submission:	06/2012
Study Completion:	07/2012
Final Report Submission:	12/2012

13. Revalidate the hold time for non-sterile cell culture media. Submit the Final Report as CBE-30 supplement.

Final Protocol Submission:	04/2013
Study Completion:	08/2013
Final Report Submission:	12/2013

14. Conduct a comprehensive risk assessment regarding the microbial control of the cell culture process and generate an action plan based on the assessment. Submit the Final Report as CBE-30 supplement.

Final Protocol Submission:	09/2012
Final Report Submission:	03/2013

15. Conduct a clinical trial to test whether the addition of hormonal therapy increases the efficacy of pertuzumab-based therapy in the hormone receptor-positive, HER2-

positive metastatic breast cancer population. Study MO27775 (PERTAIN) as designed will be completed to fulfill this post-marketing commitment.

Final Protocol Submission:	08/2012
Trial Completion:	09/2016
Final Report Submission:	03/2017

16. Submit the results of the final overall survival (OS) analysis of trial WO20698/TOC4129g as defined in your protocol Statistical Analysis Plan (SAP).

Trial Completion:	12/2013
Final Report Submission:	05/2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L JUSTICE
06/08/2012